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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,070	01/29/2007	Andrew R. Gorringe	018872.00167	6579

26712 7590 09/01/2009

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,070	GORRINGE ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-70* is/are pending in the application.

4a) Of the above claim(s) *44-50 and 61-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-59 and 70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO AMENDMENT

The amendment and response filed 6-2-09 has been entered into the record. Claims 1-43 have been cancelled Claims 44-70 are pending. Claims 51-59 and 70 are under under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Election/Restrictions

This application contains claims 44-50 and 60-69 drawn to an invention nonelected without traverse.

Rejections Withdrawn

The rejection of claims 51-59 and 70 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment to the claims.

The rejection of claims 51-56 and 70 under 35 U.S.C. 102(b) as being anticipated by Zollinger et al (US Patent 6,558,677 issued May 6, 2003) is withdrawn in view of the amendment to the claims.

The rejection of claims 51-59 and 70 under 35 U.S.C. 103(a) as being unpatentable over Zollinger et al (US Patent 6,558,677 issued May 6, 2003) in view of Foster et al (US Patent 7,384,645, with priority to December 17, 2002) is withdrawn in view of the amendment to the claims.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-59 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to using a composition comprising *Neisseria* outer membrane vesicles that are "free of *Neisseria* Opa that binds to human CEACAM1". The term "Opa" is used in the art to indicate a series of related proteins called opacity-associated proteins. The specification provides prophetic potential means of making recombinant organisms that have deleted or variant Opa. The specification teaches conventional means of making outer-membrane vesicles/blebs from *Neisseria*. The specification does not make any *Neisseria* sp. that does not have any Opa or provide outer membrane compositions that are "free" of *Neisseria* Opa that binds human CEACAM-1. CEACAM-1 is also known to the art as CD66a. The specification does not teach outer membrane vesicles that derived from *Neisseria sp* that are free of Opa that binds human CEACAM-1 or the production of a outer membrane vesicle preparation from a *Neisseria sp* that has Opa that binds human CEACAM-1. Free is an absolute standard and not one Opa protein that binds human CEACAM-1 can be present. The claims encompass outer membrane preparations from all Neisserial species including but not limited to: *N. gonorrhoeae, N. meningitidis, Neisseria cinerea, Neisseria elongata, Neisseria flavescens, Neisseria lactamica, Neisseria*

mucosa, Neisseria polysaccharea, Neisseria sicca , Neisseria subflava , Neisseria bacilliformis and Neisseria macacae . Thus, the genus is vast and the allele variation and expression heterogenous, phase variable and not characterized for the majority of the species encompassed by the claim.

The art teaches that a single strain of *Neisseria sp* can possess 3-4 (in meningococci) or 11 (in gongococci) unlinked chromosomal alleles that encode distinct Opa variants (Dehio et al, Trends in Microbiology, 6(12):489-495. December 1998). Dehio et al also teach that their transcription is phase variant and phase variation of individual loci occurs at a frequency of 10^{-3} *in vitro* constantly generating a heterogenous population of bacteria expressing none, one or multiple Opa proteins. As both intergenic and interstrain recombination between *opa* genes can occur, a vast array of alleles exists. Dehio et al teach that multiple M11 strains have different alleles expressed. The specification does not genetically characterize the *opa* alleles present in the genome of the strains used to produce outer membrane vesicles by classical means and ***human*** CEACAM-1 binding. The specification does not characterize the *opa* alleles present in the utilized strains such that the skilled artisan would have readily ascertained the that originating strain was free of all *opa* alleles such that the outer membranes produced therefrom would necessarily be free of opa that bound human CEACAM-1. The specification utilizes immunoblotting and ELISA binding assay to determine CEACAM-1 binding (see Figure 2 A and B). The CEACAM-1 binding assays are not characterized as human CEACAM-1 and it is noted that Opa52 is an *opa* allele that binds CD66a (CEACAM-1) but is not characterized as either mouse or human. Furthermore, both Figure indicate that even in the alleged Opa(-) strain, there are outer-membrane vesicles present that bind CEACAM-1. The skilled artisan would recognize that antibody immunoblotting and CEACAM-1 binding ELISA assays, while sensitive, do not have the capability of detection of a single Opa protein binding CEACAM-1 or human CEACAM-1 in particular. Given the known phase variation of *opa* alleles, the presence of multiple alleles in the M11 strain of the specification and the lack of showing

in the specification of a *Neisseria* outer membrane preparation that is *free* of Opa that binds human CEACAM-1, the skilled artisan would recognize that Applicants were not in possession of the claimed composition for use in the method of treatment of prevention of meningococcal disease.

Claims 51-59 and 70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to treatment or prevention of meningococcal disease encompassing diseases caused by *Neisseria meningitidis* including meningococcal meningitis and meningococcemia. The method of treatment/prevention uses outermembrane vesicles that are "free of Neisseria Opa that binds to human CEACAM1". The term "Opa" is used in the art to indicate a series of related proteins called opacity-associated proteins. The specification provides prophetic potential means of making recombinant organisms that have deleted or variant Opa. The specification teaches conventional means of making outer-membrane vesicles/blebs from *Neisseria*. The specification does not make any *Neisseria* sp. that does not have any Opa or provide outer membrane compositions that are "free" of *Neisseria* Opa that binds human CEACAM-1. CEACAM-1 is also known to the art as CD66a/biliary glycoprotein. (http://www.genecards.org/cgi-bin/carddisp.pl?gene=CEACAM1) The specification does not teach outer membrane vesicles that derived from *Neisseria sp* that are free of Opa that binds human CEACAM-1 or the production of a outer membrane vesicle preparation from a *Neisseria sp* that has Opa that binds human CEACAM-1. Free is an absolute standard and not one Opa protein that binds human CEACAM-1 can be present. The claims encompass outer membrane preparations from all Neisserial species including but not limited to: *N. gonorrhoeae, N. meningitidis, Neisseria cinerea, Neisseria elongata, Neisseria flavescens, Neisseria lactamica, Neisseria*

mucosa, Neisseria polysaccharea, Neisseria sicca , Neisseria subflava , Neisseria bacilliformis and Neisseria macacae . Thus, the genus is vast and the allele variation and expression heterogeneous, phase variable and not characterized for the majority of the species encompassed by the claim.

The art teaches that a single strain of *Neisseria sp* can possess 3-4 (in meningococci) or 11 (in gongococci) unlinked chromosomal alleles that encode distinct Opa variants (Dehio et al, Trends in Microbiology, 6(12):489-495. December 1998). Dehio et al also teach that their transcription is phase variant and phase variation of individual loci occurs at a frequency of 10^{-3} *in vitro* constantly generating a heterogenous population of bacteria expressing none, one or multiple Opa proteins (page 489, column 2). As both intergenic and interstrain recombination between *opa* genes can occur, a vast array of alleles exists. Dehio et al teach that multiple M11 strains have different alleles expressed. The specification does not genetically characterize the *opa* alleles present in the genome of the strains used to produce outer membrane vesicles by classical means and ***human*** CEACAM-1 binding. Since the genetic opa alleles are not characterized in the strains used in the specification, the skilled artisan could not make outer membrane preparations using the claissical methods described by the specification and the art to arrive at an outer membrane fraction/preparation/vesicle/bleb etc that is by definition "free of Opa that binds human CEACAM-1". The specification suggests that conventional knock out and mutational strategies that can be used to make strains that are free of Opa that binds human CEACAM-1. This is not persuasive, because the specification does not teach the allele structure of the strains used, many of the species of Neisseria are not characterized with respect to Opa alleles that bind human CEACAM-1 or CEACAM-1 in particular. Therefore, targeted knock out strategies in the specification and targeted mutational strategies could not be readily and immediately employed by the skilled artisan to make such. One skilled in the art would have to go forth and specifically characterized the molecular nucleic acid sequences of all the *opa* alleles in a particular strain of

Neisseria, design knock out or mutational strategies and then perform one or multiple mutations to even begin to arrive at a strain that has the requisite property of not having *opa* alleles that bind human CEACAM-1. The characterization of alleles, the nucleic acid sequencing, the design of multiple mutational and knock out strategies of a particular *Neisseria* species, before testing for use as a vaccine for treatment/prevention of meningococcal disease is far outside the relm of routine experimentation. Such, experimentation is not routine and predictable. The other mutational strategies suggested, but not performed are generic non-targeted methods of mutation and subsequent selection of non human CEACAM-1 binding. This methodology is similarly flawed because: (1) presence of multiple *opa* alleles; (2) phase variation of in any culture of Opa proteins; (3) assays not sufficient sensitive to detect a single human -CEACAM 1 binding Opa protein in an outer membrane vesicle and (4) lack of characterization of alleles present in the strains of the specification such that genetic characterization can be used to determine production or lack thereof of any human CEACAM-1 binding Opa protein by the mutant strain.

In view of the lack of teaching of a *Neisserial* outer membrane vesicle preparation, free of Opa proteins that bind human CEACAM-1, the lack of described assays with sufficient sensitivity to detect a single human CEACAM-1 - binding Opa protein, the lack of teaching of any *Neisserial* mutant with the genetic make up of lacking Opa proteins or lacking Opa proteins that bind human CEACAM-1, it is concluded that one skilled in the art would not be able to make and use the invention as now claimed.

Status of Claims

Claims 51-59 and 70 stand rejected. Claims 44-50 and 60-69 are withdrawn from consideration.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisors, Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/

Primary Examiner